201-14748A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

DIISOPROPYLBENZENE CATEGORY

TEST PLAN
(Revised)

m-DIISOPROPYLBENZENE [CAS Registry No. 99-62-7]
p-DIISOPROPYLBENZENE [CAS Registry No. 100-18-5]
DIISOPROPYLBENZENE [CAS Registry No. 25321-09-9]

PREPARED BY:

THE AMERICAN CHEMISTRY COUNCIL'S
HYDROQUINONE PRECURSORS AND DERIVATIVES PANEL
DIISOPROPYLBENZENE TASK FORCE

MEMBER COMPANIES OF THE TASK FORCE:
EASTMAN CHEMICAL COMPANY
GEORGIA GULF CORPORATION
GOODYEAR RUBBER AND TIRE COMPANY
KOCH SPECIALTY CHEMICAL COMPANY; a division of KOCH PETROLEUM GROUP, L.P.

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TABLE OF CONTENTS

OVERVIEW

The diisopropylbenzene (DIPB) category consists of a group of three chemicals consisting of CAS Registry Numbers 99-62-7, 100-18-5, and 25321-09-9. Two of the three members, meta-DIPB and para-DIPB, are pure isomers while the third member is a Class II chemical consisting of a mixture of all three ortho-, meta-, and para-DIPB isomers (xDIPB). In preparing this test plan, the Hydroquinone Precursors and Derivatives Panel has given careful consideration to the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999. As directed by EPA in that letter, the Panel has sought to maximize the use of existing data for scientifically appropriate related chemicals and structure-activity-relationships. Additionally, and also as directed in EPA's letter, in analyzing the adequacy of existing data, the Panel has conducted a thoughtful, qualitative analysis rather than use a rote checklist approach. It is the intent of the Panel to fulfill all the Screening Information Data Set (SIDS) endpoints of the HPV program through the use of data that are already in existence. For the DIPB category, this data set consist of results from studies conducted specifically on either one of the pure meta- and or para-isomers, or with results from studies conducted on xDIPB (the mixture of all three isomers). In addition, some endpoints have been completed through the utilization of data from studies conducted on structurally similar compounds and from modeling programs accepted by the EPA. The Panel believes these data are adequate to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests.

SUMMARY OF TEST PLAN AND DATA

The diisopropylbenzene (DIPB) category consists of a group of three chemicals consisting of CAS Registry Numbers 99-62-7, 100-18-5, and 25321-09-9. Two of the three members, meta-DIPB and para-DIPB, are pure isomers while the third member is a Class II chemical consisting of a mixture of all three ortho-, meta-, and para-DIPB isomers (xDIPB). At this time the sole commercial use for the individual pure DIPB isomers are as industrial intermediates in the synthesis of other chemicals. Similarly, commercial applications for xDIPB are primarily as a raw material for chemical manufacture; however, it is also used as a component in an industrial cleaning formulation. Therefore, no isomer of DIPB is known to be distributed in commerce for any non-industrial uses or applications in consumer products. Purposeful production of DIPB occurs through the alkylation of benzene with propylene in the presence of a catalyst, followed by distillation to meet purity specifications. Some mixed DIPB is formed as a by-product in the manufacture of cumene (mono-isopropylbenzene) where part of the cumene is further alkylated with available propylene to form xDIPB.

In general, the individual meta- and para-isomers are quite pure when sold (mDIPB purity is >95% and pDIPB is >99%), with the primary contaminants consisting of various other DIPB isomers. The mixed isomer category member, xDIPB, typically contains an average of 2.4%, 55.8%, and 34.5% of the respective *ortho-*, *meta-*, and *para-*DIPB isomers. xDIPB may contain small amounts of cumene and other aromatic hydrocarbon impurities. They are all manufactured and transported in closed systems and have a very limited number of customers who also handle them in closed systems. Occupational exposure to DIPBs is minimized by the manner in which they are manufactured and through good industrial hygiene practices. Routine exposure to the general population is not anticipated. Significant environmental exposures from their manufacture and use are unlikely except under conditions of a spill incident.

The three DIPB CAS numbers that constitute the DIPB category the Panel is submitting are very similar from a structural standpoint as they are all isomers of the same compound and possess nearly identical physical-chemical properties. In addition, all available hazard data indicate these substances induce a similar toxicological profile following either acute or repeated exposures, with the liver and kidney being the primary target organs. Accordingly, the Panel believes that data generated on any one of the individual isomers as well as data from studies conducted on the mixture itself (xDIPB) can be used interchangeably in the evaluation of their environmental fate, ecotoxicity, and mammalian toxicity potentials (See Table 1).

In addition to the interchangeable use of data from the various DIPB compounds to substitute for each other, there was a need for the utilization of data from various other short chain mono- and di-alkylated benzene compounds. Specifically, these other surrogates consisted of either isopropylbenzene, ethylbenzene, or various diethylbenzene isomers (ortho-, meta-, and para-). These other alkylbenzene compounds were used to assess hydrolytic degradation potential, ability to impact algae growth, and in the determination of the potential for DIPB to induce reproductive and/or developmental toxicity. The Panel believes the use of these compounds as surrogates is valid based on their structural, physical-chemical, and metabolic similarities to DIPB. DIPB and the aforementioned surrogates are predominantly metabolized via oxidation reactions on the alkyl side chain followed by conjugation reactions. In addition, these compounds share with the various DIPBs a similar acute toxicity potential and target organ specificity (liver and kidney) following repeated exposure (See Table 1).

Data assessing the various physical-chemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for the different DIPB isomers were obtained from either reputable textbooks, actual study data, or from computer estimation modeling programs accepted by EPA and found in EPIWIN (Version 1.2, Syracuse Research Corporation, Syracuse, NY). These data indicate that the DIPBs are liquids at room temperature with a low potential to volatilize. They are essentially insoluble in water but highly soluble in organic solvents. The quality of the available information meets the requirements of the various endpoints to preclude the need for any additional physical and chemical properties testing.

Data from studies conducted on the various DIPBs, structurally similar compounds, or estimation modeling programs accepted by EPA were available, and of sufficient quality to complete the assessment of all the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity). Overall, due to its low volatility, fugacity estimations predict that DIPB will distribute primarily to soil and water. Available data indicate DIPB is not readily degraded or even soluble in these two media. Although its release into the environment

would primarily occur through fugitive emissions and evaporative mechanisms, atmospheric hydroxyl radicals are predicted to readily break down the molecule. In addition, data from a study assessing its volatility from water demonstrated that there is a 100% loss from an aqueous saturated solution after 96 hours (Unpublished 1986 Kodak report).

The toxic potential of DIPB to fish and aquatic invertebrates was determined through studies using both mDIPB and pDIPB, and its potential to affect algae growth was evaluated through the use of modeling. Modeling results were then compared to actual studies conducted on two structurally similar surrogate compounds (isopropylbenzene and 1,4-diethylbenzene). In total, these data demonstrate DIPBs are not toxic to these particular organisms at concentrations that are either at, or near, their saturation point in water. Coupled with the extremely low water solubility of DIPBs, the potential for exposure of these substances to aqueous organisms is also very unlikely due to its primary use as an industrial intermediate.

The potential to induce toxicity in mammalian species following acute oral exposures is very low and, as previously noted, the potential for human exposure is believed to be quite limited. The results of studies conducted on both isomers and the mixture indicate these materials are only slightly toxic with LD50 values ranging from >3200 mg/kg to >5000 mg/kg. Data were available on all three CAS numbers evaluating their effects following repeated oral exposures with exposure durations ranging from 12 to 28 days. Results of these studies demonstrated that the pure isomers and the mixture induce effects in the stomach (nonspecific irritation), liver (weight increase in absence of any changes in morphological appearance) and kidney (hyaline droplet accumulation). These changes were most prominent at the highest dose levels. Such effects in the liver are often considered as an adaptive response by the animals to the high dose levels of chemical they are receiving. This effect reversed itself following a 14-day recovery period. The changes noted in the kidney were specific to males and are interpreted to be due to accumulation of alpha-2u-globulin protein. Accumulation of this protein in the kidney and its pathological consequences are unique to the rat species and are not believed to be of concern for humans who lack this protein. Evidence of a localized gastric irritation was also noted in some studies. This effect is believed to be due to the manner in which the animals received the test material (i.e., as a single large oral bolus), resulting in a small surface area of tissue exposed to a high concentration of test material. Several mono- and di-alkylbenzene compounds were utilized as structural surrogates to assess the potential of DIPB to induce developmental and reproductive toxicity. The Panel utilized a well-recognized reproductive toxicology expert to assess the validity of this approach. It was the opinion of this expert that "additional studies on analogs or indeed, the diisopropylbenzene isomers themselves, would only serve the limited objective of confirming the absence of hazard to reproductive and developmental toxicity at reasonable oral or inhalational exposures." Results from several different studies conducted on DIPB as a mixed isomer indicate that these compounds do not induce genotoxicity.

In conclusion, the Panel believes that it has completed adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted specifically on either the pure meta- and/or para-DIPB isomers themselves, or with results from studies conducted with the mixed isomers. Where appropriate, some endpoints have been filled through the utilization of data from studies conducted on structurally similar compounds and from modeling programs accepted by the EPA. The summarized data indicate that these chemicals, as used in commerce, constitute a low risk to both workers and the general population.

TEST PLAN FOR DIISOPROPYLBENZENES

I. Category Justification and Use of Surrogate Data

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999a). The chemicals that comprise the three CAS numbers that form the Panel's category are structurally similar as they are all isomers of DIPB. As seen in Table 1 below, all three CAS numbers have very similar physical-chemical properties, and induce a similar toxicological profile following either acute or repeated exposure, with the liver and kidney being the major target organs. Accordingly, the Panel believes that data from an individual pure isomer or data from studies conducted on the entire mixture of all isomers (xDIPB) may be used interchangeably to complete the hazard assessment for any specific endpoint.

In addition to the interchangeable use of data from different DIPB isomers to complete some endpoints, there is also a need for the use of surrogate data from various other short chain mono- and di-alkylated benzene compounds to assess the potential for DIPB to induce reproductive and developmental toxicity. Specifically, the compounds isopropylbenzene (cumene), ethylbenzene, o-, m-, and p-diethylbenzene are believed to meet the criteria needed to allow for their use as surrogates in assessing reproductive and developmental toxicity. As is readily seen below in Table 1, these compounds are all very similar in structure, physical-chemical properties, acute toxicity potential, as well as target organ specificity following repeated exposures.

Results of metabolism studies conducted on various alkylated benzene compounds indicate that these types of compounds undergo similar routes of metabolic reactions. These reactions are characterized by phase I biotransformations on the alkyl side-chain to form alcohols and/or carboxylic acids. These metabolites are eventually eliminated in the urine following phase II transformations as conjugates of glucuronic acid or glycine (Williams, 1959, Bakke and Scheline, 1970). With ethylbenzene, the principal metabolic pathway in rats is believed to be the same as in humans (Climie *et al*, 1983), and its metabolites in animals has been shown to be similar without regard to route of exposure (Climie *et al*, 1983). Similarly with cumene, very similar rates of metabolism of the chemical and routes of elimination were observed for oral and inhalation exposures in animals (Bushy Run Research Centre, 1989c). Unfortunately, at this time, metabolic data specifically on DIPBs are not available. While it is possible that hydroxylation reactions on the aromatic ring may take place to form phenols, there is no evidence reported that these types of compounds would undergo complete dealkylation reactions in order to form benzene. Thus, overall, the question of toxicity induced by the metabolic hydroxylation to phenols is mitigated owing to the small quantities of metabolites involved and partly to their subsequent rather quick conversion to glucuronides and etheral sulfates (Bakke and Scheline, 1970).

The Panel sought an independent review by Mr. James Schardein, an independent consultant formerly employed by WIL Research Laboratories, Inc., and expert in reproductive toxicology, to determine the appropriateness of data from surrogate chemicals to complete the reproductive and developmental toxicity endpoints. Mr. Schardein concluded that the approach the Panel took in regard to utilizing surrogates for these specific endpoints was appropriate and that the data from the surrogates was of sufficient quality to fulfill the required endpoints. The following are excerpts from Mr. Schardein's review (Attachment I).

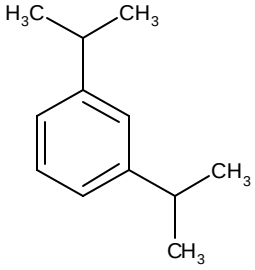
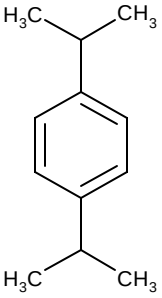
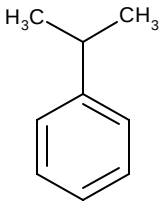
"I consider the chemicals selected to serve as surrogates to be a valid approach in fulfilling the reproductive/developmental endpoint evaluation for the diisopropylbenzenes, since acceptable data exists on these chemicals (see following)."

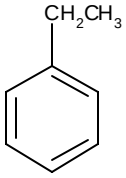
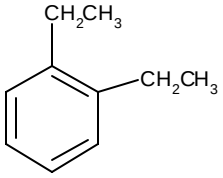
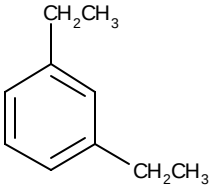
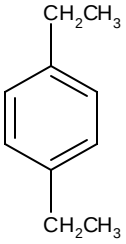
"The existent *developmental toxicity* studies in one (oral route) and three (inhalation route) species with the alkylbenzene analogs demonstrate quite convincingly the potential for developmental toxicity in laboratory species. The SIDS requirement is, in fact, for one species testing. In my judgment, no further developmental toxicity studies on the candidate diisopropylbenzene chemicals are needed, as the data on the surrogates suffices. The present data available for interpretation are fully adequate; no data gaps are evident, and additional studies would add little to the database already gleaned from the completed studies with respect to effects on development, by either route of exposure, oral or inhalation. The more critically conducted and robust studies evaluated (Bushy Run Research Centre, 1989; Saillenfait et al, 1999) on the 1,2-DEB and cumene analogs indicate embryotoxicity at maternally toxic levels, but no teratogenicity."

"The results with the *reproductive toxicity* studies conducted on the diisopropylbenzene analogs are less perfect. In fact, only the data from the study conducted on 1,4-DEB is suitable for adequate characterization of the *conventional* reproductive toxicity assessment of diisopropylbenzene analogs. The remaining two studies, conducted on cumene and ethylbenzene, were not conceived with the objective of fully characterizing their reproductive toxicity potential. However, it cannot be stressed too emphatically, that the studies on the latter two analogs provide much valuable information on the reproductive process in other ways. In both the cumene 90-day inhalation toxicity study in rats and in the ethylbenzene 28-day inhalation toxicity study in three species (see Table 4), alternative study designs that have been considered in the past as acceptable in the SIDS testing scheme, are more than adequate, since there was assessment of the reproductive organs (without mating trial). No toxicity was reported in either study with respect to histopathology of the testes, testicular weight, or the process of spermatogenesis (as evidenced by spermatid quantitation and sperm staging) at exposure levels greater than 1200 ppm in the case of cumene, or greater than 782 ppm (rodents) or 1610 ppm (rabbit) with respect to ethylbenzene. Ovarian toxicity was also assessed in the latter study (and was not demonstrated). These data, coupled with the fact that conventional reproductive toxicity tests in rodents for fertility are an insensitive indicator of reproductive risk in humans (Working, 1988), indicate satisfactory testing. Additionally, testicular histopathological assessments and sperm assessment, which have the highest detection rates for male reproductive effects in animal models (Linder *et al*, 1992; Ulbrich and Palmer, 1995), provide substantial evidence that the reproductive data available for the analogs will suffice to characterize the absence of reproductive effects for the analogs, as well as the diisopropylbenzenes, for which they act as surrogates. It is illogical in my opinion to assume that additional studies beyond what data is provided in the assessment made in this document would be required to establish further the safety shown in the studies evaluated."

"It appears to this reviewer that additional studies on analogs or indeed, the diisopropylbenzene isomers themselves, would only serve the limited objective of confirming the absence of hazard to reproductive and developmental toxicity at reasonable oral or inhalational exposures." (See Appendix I)

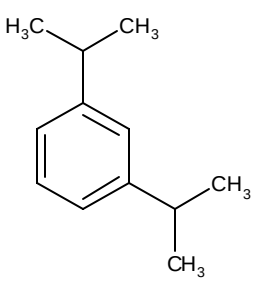
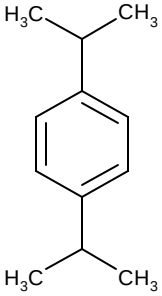
Table 1: Matrix of DIPB and Chemical Surrogates

			DIPB Mixed Isomers	
Common Name	m-Diisopropylbenzene (mDIPB)	p-Diisopropylbenzene (pDIPB)	Diisopropylbenzene (xDIPB)	Cumene (Isopropylbenzene)
CAS No.	99-62-7	100-18-5	25321-09-9	98-82-8
<u>Physico-Chemical</u> Melting Point Boiling Point Density/Sp. G. Vapor Pressure Partition Coeff. Water Solubility	 -61 C 203.2 C 0.86 1 mmHg at 34.7 C 4.9 7 ppm	 -17.1 C 210.3 C 0.86 1 mmHg at 40 C 3.45 3 ppm	 -40 C 205 C 0.9 0.25-0.39 mmHg at 25C 4.9 4.3 ppm	 -96 C 152.4 C 0.86 4.5 mmHg at 25 C 3.66 50 ppm at 25 C
Acute Toxicity	>5,000 mg/kg	>5 mg/kg	3,900 mg/kg	2000-4000 mg/kg
Repeat Dose – Target Organs (Oral exposure)	Liver and Kidney	Liver	Liver and Kidney	Liver and Kidney

				
Common Name	Ethylbenzene	o-Diethylbenzene	m-Diethylbenzene	p-Diethylbenzene
CAS No.	100-41-4	135-01-3	141-93-5	105-05-5
<u>Physical-Chemical</u> Melting Point Boiling Point Density/Sp. G. Vapor Pressure Partition Coeff. Water Solubility	 -95 C 136.2 C 0.867 10 mmHg at 26 C 3.15 140 ppm at 15 C	 -31.2 C 183.4 C 0.88 at 20 C 1.1 mmHg at 25 C No Data 71 ppm at 25 C	 -83.89 C 181 C 0.862 at 20 C 1.13 mmHg at 25 C 4.5 170 ppm (temp not stated)	 -42.8 C 183.8 C 0.86 1.1 mmHg at 25 C 2.87 25 ppm at 25 C
Acute Toxicity	3,900 mg/kg	1,200 mg/kg	1,200 mg/kg	>2000 mg/kg
Repeat Dose – Target Organs	Lung (inhalation exposure), Liver, and Kidney	No Data Available	No Data Available	Liver and Kidney (Oral exposure)

The above data for the DIPB surrogates were obtained from references found in the Hazardous Substances Database (HSDB). Information on the DIPB compounds is referenced within the robust summaries.

II. Matrix of Available Data and Proposed Data Development for Chemicals in the DIPB Category

OECD SIDS Endpoints			DIPB (Mixed isomers)
	m-Diisopropylbenzene	p-Diisopropylbenzene	o-, m-, p-
PHYSICAL-CHEMICAL DATA			
Melting Point	Y[1]	Y	Y
Boiling Point	Y	Y	Y
Vapor Pressure	Y	Y	Y
Partition Coefficient	E[2]	E	E
Water Solubility	Y	Y	E
ENVIRONMENTAL FATE ENDPOINTS			
Photodegradation	E	E	E
Stability in Water	SAR[3]	SAR	SAR
Biodegradation	SAR	Y	Y
Fugacity	E	E	E
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	SAR
Acute Toxicity to Aquatic Invertebrates	Y	Y	SAR
Toxicity to Aquatic Plants	E/SAR	E/SAR	E/SAR
TOXICOLOGICAL DATA			
Acute Toxicity	Y	Y	Y
Repeated Dose Toxicity	Y	SAR	Y
Genetic Toxicity – Mutation	SAR	SAR	Y
Genetic Toxicity – Chromosomal Aberrations	SAR	SAR	Y
Developmental Toxicity	SAR	SAR	SAR
Toxicity to Reproduction	SAR	SAR	SAR
OTHER TOXICITY DATA			
Genetic Toxicity – Primary DNA Damage			Y
Cell transformation Assay			Y

1. Y = Yes, study data specifically on that chemical are available.
2. E = Endpoint was completed through EPA recommended estimation/calculation models.
3. SAR = Endpoint is filled using data from a structurally similar chemical(s).

III. Description of the Test Plan for Each SIDS Endpoint for Each Chemical

Physicochemical Properties

Melting point - **mDIPB -** A value for this endpoint was obtained from reputable textbook.
pDIPB - A value for this endpoint was obtained from reputable textbook.
xDIPB - A value for this endpoint was obtained from MPBPWIN, a computer estimation program in EPIWIN.

Technically data are not needed as these chemicals are liquids with likely melting points of <0 C.

Boiling Point - **mDIPB -** A value for this endpoint was obtained from reputable textbook.
pDIPB - A value for this endpoint was obtained from reputable textbook.
xDIPB - A value for this endpoint was obtained from reputable textbook.

Vapor Pressure - **mDIPB -** A value for this endpoint was obtained from reputable textbook.
pDIPB - A value for this endpoint was obtained from reputable textbook.
xDIPB - A value for this endpoint was obtained from reputable textbook.

Partition Coefficient - **mDIPB -** A value for this endpoint was obtained from KOWIN, a computer estimation program.
pDIPB - A value for this endpoint was obtained from KOWIN, a computer estimation program.
xDIPB - A value for this endpoint was obtained from KOWIN, a computer estimation program.

Water Solubility - **mDIPB -** A value for this endpoint was obtained by an OECD-TG105 study.
PDIPB - A value for this endpoint was obtained by an experimental study.
xDIPB - A value for this endpoint was obtained from WSKOW v 1.40; a computer estimation program.

Conclusion: **No additional tests are proposed as all end points are satisfied by data from reputable textbooks, actual studies, or acceptable computer modeling estimation programs.**

Environmental Fate

Photodegradation - **mDIPB -** A value for this endpoint was obtained using AOPWIN, a computer estimation program.
pDIPB - A value for this endpoint was obtained using AOPWIN, a computer estimation program.
xDIPB - A value for this endpoint was obtained using AOPWIN, a computer estimation program.

Stability in Water - **mDIPB -** This endpoint is filled with data from an OECD TG-111 study with 1,4 diethylbenzene, a surrogate dialkylbenzene chemical.
pDIPB - This endpoint is filled with data from an OECD TG-111 study with 1,4 diethylbenzene, a surrogate dialkylbenzene chemical.
xDIPB - This endpoint is filled with data from an OECD TG-111 study with 1,4 diethylbenzene, a surrogate dialkylbenzene chemical.

Biodegradation - **mDIPB -** This endpoint was satisfied through the use of data from studies conducted on pDIPB, xDIPB, and 1,4-diethylbenzene.
pDIPB - This endpoint was satisfied through the use of study data on pDIPB and is further supported by data from studies conducted on xDIPB, and 1,4-diethylbenzene.
xDIPB - This endpoint was satisfied through the use of study data on xDIPB and is further supported by data from studies conducted on pDIPB, and 1,4-diethylbenzene.

Fugacity - **mDIPB -** Transport between environmental compartments was determined by using EPIWIN: EQC Level III fugacity computer model.
pDIPB - Transport between environmental compartments was determined by using EPIWIN: EQC Level III fugacity computer model.
xDIPB - Transport between environmental compartments was determined by using EPIWIN: EQC Level III fugacity computer model.

Conclusion: **No additional tests are proposed as all endpoints have been satisfied using data from studies conducted on the various DIPBs, structurally similar compounds, or acceptable computer modeling estimation programs.**

Ecotoxicity Data

Acute Toxicity to Fish - **mDIPB -** This endpoint is filled by data from an OECD TG-203 study.
pDIPB - This endpoint is filled by data from a study that followed a protocol similar to OECD TG-203.
xDIPB - This endpoint is filled by data from mDIPB and pDIPB.

Acute Toxicity to Aquatic Invertebrates - **mDIPB -** This endpoint is filled by data from an OECD TG-202 study.
pDIPB - This endpoint is filled by data from a study that followed a protocol similar to OECD TG-202.
xDIPB - This endpoint is filled by data from mDIPB and pDIPB.

Toxicity to Aquatic Plants - **mDIPB** - This endpoint is filled by data developed by ECOSAR, a computer modeling program, along with data from an OECD TG-201 study on the surrogate chemicals isopropylbenzene and 1,4-diethylbenzene.
pDIPB - This endpoint is filled by data developed by ECOSAR, a computer modeling program, along with data from an OECD TG-201 study on the surrogate chemicals isopropylbenzene and 1,4-diethylbenzene.
xDIPB - This endpoint is filled by data developed by ECOSAR, a computer modeling program, along with data from an OECD TG-201 study on the surrogate chemicals isopropylbenzene and 1,4-diethylbenzene.

Conclusion: **No additional testing is proposed as all endpoints have been satisfied using quality data from studies conducted on the various DIPBs, or through the use of computer modeling in conjunction with actual studies on structurally similar compounds.**

Toxicological Data

Acute Toxicity - **mDIPB -** This endpoint is filled by data from an oral study on mDIPB that followed established protocols under GLP assurances.
pDIPB - This endpoint is filled by data from an oral study on pDIPB that followed established protocols.
xDIPB - This endpoint is filled by data from an oral study on xDIPB that followed established protocols.

Repeat Dose Toxicity -	**mDIPB -** This endpoint is filled with data from an OECD: TG-407 (and Annex V B.7.) 28-Day repeated exposure study conducted on mDIPB under GLP assurances. **pDIPB -** This endpoint is filled with data from a 14-Day repeated exposure study conducted on pDIPB. Target organs identified in this study were similar to ones identified following exposure to mDIPB and xDIPB for 28 days. **xDIPB -** This endpoint is filled with data from a 28-day repeated exposure study conducted on xDIPB that was noted to have followed Japanese guidelines and GLP assurances.
Genetic Toxicity Mutation -	**mDIPB -** This endpoint is filled using surrogate data from two studies conducted on xDIPB under GLP assurances. **pDIPB -** This endpoint is filled using surrogate data from two studies conducted on xDIPB under GLP assurances. **xDIPB -** This endpoint is filled using data from two studies conducted on xDIPB under GLP assurances. One study assessed mutations in *Salmonella typhimurium* and *E. coli* (Ames Assay) and the other evaluated the induction of forward mutations in Chinese hamster ovary cells (CHO/HGPRT). In the Ames assay, xDIPB was noted to be pure mixture. In the CHO/HGPRT study, the chemical utilized was a mixture that historically has contained only 25-40% mixed DIPB isomers.
Aberration -	**mDIPB** - This endpoint is filled using surrogate data from two studies conducted on xDIPB under GLP assurances. **pDIPB** - This endpoint is filled using surrogate data from two studies conducted on xDIPB under GLP assurances. **xDIPB** - This endpoint is filled using data from two studies conducted on xDIPB under GLP assurances. One study was an *in vitro* OECD: TG-473 study, while the other was an *in vivo* mouse micronucleus assay. In the TG-473 study xDIPB was noted to be a pure mixture. In the micronucleus assay, the chemical utilized was a mixture that historically has contained 25-40% mixed DIPB isomers.
Primary DNA Damage -	While not a HPV SIDS endpoint, a robust summary was prepared relative to the potential of a mixture that historically has contained 25-40% mixed DIPB isomers to induce unscheduled DNA synthesis in rat hepatocytes using a protocol identical to an OECD TG-482 study. This study was conducted under GLP assurances.
Developmental and Reproductive Toxicity -	**mDIPB, pDIPB, xDIPB** - This endpoint is filled using surrogate data from studies conducted on various mono- and di-alkyl benzene compounds (isopropylbenzene, ethylbenzene, o-, m-, and p-diethylbenzene). An independent reproductive toxicology consultant validated the scientific suitability for the use of these chemicals and their credibility. His review and assessment can be found in Attachment I. It was his conclusion that additional studies beyond what data are currently available would likely not be useful.
Conclusion:	**No additional testing is proposed as all endpoints have been satisfied with quality data from studies conducted using either one or two of the pure DIPB isomers, on DIPB as a mixed-isomer compound (xDIPB), or from studies on several surrogate chemicals.**

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (USEPA 1999b) and the systematic approach described by Klimisch *et al*. (1997). These methods include consideration of the reliability, relevance, and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies as recommended by the EPA (USEPA 1999b). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

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OECD SIDS Document: Section 3. Data Evaluation, Preparation of SIDS Dossiers and Testing Plans

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